

REMARKS/ARGUMENTS

Reexamination and reconsideration of this Application, withdrawal of the rejections, and formal notification of the allowability of all claims as now presented are earnestly solicited in light of the remarks that follow. Claims 16-30 are pending in the application.

Claims 16-30 stand rejected under 35 U.S.C. §103(a) as being unpatentable over the combined teachings of U.S. Patent No. 5,484,601 to O'Leary *et al.*, U.S. Patent No. 5,385,887 to Yim *et al.*, and the WO 98/40113 reference listing Wironen as an inventor. The Office Action relies upon the O'Leary reference as teaching a composition comprising demineralized bone powder, an organic liquid carrier and, optionally, a thickening agent such as methylcellulose. The Office Action relies upon the Yim reference as disclosing a composition for delivering osteogenic proteins that contains calcium sulfate hemihydrate. The Examiner has taken the position that it would have been obvious to include the calcium sulfate taught in Yim in the composition described in O'Leary because both patents are directed to bone growth promoting compositions and Yim teaches that calcium sulfate improves handling, moldability, and consistency in such a composition. The Examiner relies upon the Wironen reference as disclosing a bone paste that may comprise cancellous bone chips. The Examiner alleges that it would have been obvious to one of ordinary skill in the art to modify the O'Leary composition to include cancellous bone chips based on the teachings of the Wironen reference. Applicants respectfully traverse this rejection.

Applicants respectfully submit that one of ordinary skill in the art would have no motivation to combine the three references of the rejection in the manner contemplated by the Examiner. Specifically, the art provides no motivation for combining the Yim and Wironen references with the O'Leary reference in the manner relied upon by the Examiner.

The O'Leary reference is directed to a flowable composition comprising demineralized bone powder and an organic liquid carrier, and suggests that a thickener may be added to the composition to maintain the bone powder in suspension. The O'Leary reference teaches that the composition can be applied to the site of a bone defect in the form of, for example, a highly viscous paste. Thus, the O'Leary reference is directed to a composition designed to provide demineralized bone powder in a form suitable for surgical use.

The Examiner relies on language in the Yim reference regarding reduction in set-up time and improvement in handling, moldability and consistency as evidence of a motivation to combine the calcium sulfate hemihydrate of Yim with the formulation of O'Leary (page 10 of Official Action mailed 7/2/02; pages 6-7 of Official Action mailed on 4/2/03). However, Yim does not provide a general suggestion that calcium sulfate provides such advantages in all bone graft compositions. Instead, the Yim reference only suggests that a calcium sulfate hemihydrate-containing substance (CSHS) provides such advantages when combined with the formulation described in U.S. Pat. No. 5,171,579 (see column 2, lines 51-65). Yim only suggests a CSHS provides such advantages in the context of a formulation comprising osteogenic proteins, autogenous blood, and a porous particulate polymer matrix, such as a copolymer of lactic acid and glycolic acid (PLGA). There is no suggestion in the Yim reference that such improved properties would be expected in any other formulation. Yim merely teaches that, "[t]o reduce the preparation time and improve the above formulation's handling characteristics"(emphasis added), a CSHS can be added. The "above formulation" is the formulation described in the '579 patent, which includes an osteogenic protein, autogenous blood, and a porous particulate polymer matrix. Since the composition in the O'Leary reference is not a combination of osteogenic proteins with autogenous blood and a porous particulate polymer matrix such as PLGA, there would be no motivation to combine the CSHS of Yim with the composition described in O'Leary for the reasons suggested by the Examiner. The O'Leary formulation comprises demineralized bone powder and an organic liquid, and such a composition is markedly dissimilar to the composition described in Yim as needing improvement in set-up time, moldability, etc. Further, there is nothing in the O'Leary reference to suggest a problem with moldability, consistency, etc. of the formulation described therein that might lead one of ordinary skill in the art to seek an additive to address such a problem. Indeed, the O'Leary patent seems to suggest that the consistency of the "flowable" material can be adjusted simply by altering the amount of the liquid component (column 3, lines 28-35).

In a further effort to bolster the proposed combination of Yim with O'Leary, the Examiner notes that there is no suggestion in the O'Leary reference that "it will become inoperative" with the inclusion of further ingredients, and notes that the O'Leary reference even

contemplates the addition of certain ingredients. Similarly, the Examiner argues that the Yim and O'Leary formulations are "sufficiently similar" such that one of ordinary skill would be aware that calcium sulfate hemihydrate "would not impair or otherwise negatively affect" the O'Leary composition. However, the simple understanding by one of ordinary skill in the art that the addition of a certain compound to a composition would not negatively affect that composition is insufficient to motivate one to make such a combination. The art must provide a positive motivation to make the combination suggested in the rejection rather than simply fail to teach against such a combination.

The Examiner also relies on a general recitation in O'Leary that "a variety of substances" can be added to the bone particles. However, such a broad and non-specific reference to optional ingredients, even one that mentions the addition of "inorganic elements", is clearly insufficient to provide the requisite motivation to include a specific inorganic compound such as calcium sulfate hemihydrate. Such a general teaching really has no bearing at all on the specific question of whether one of ordinary skill in the art would have been motivated to combine the calcium sulfate hemihydrate teaching of Yim with the formulation in O'Leary.

Thus, as noted above, it is respectfully submitted that one of ordinary skill in the art would have no motivation to combine the teachings of Yim with the teachings of O'Leary as contemplated by the Examiner and Applicants respectfully request reconsideration and withdrawal of the rejection of record for this reason.

In addition, Applicants respectfully submit that there is no motivation to combine the teachings of the Wironen reference with the teachings of either O'Leary or Yim. Although the Examiner alleges that the O'Leary and Yim compositions are similar, Applicants note that no such general assertion of similarity is made with respect to Wironen and the remaining references of record, and for good reason. The composition described in the Wironen reference is so fundamentally distinct from the compositions described in the Yim and O'Leary references that one of ordinary skill in the art would clearly view such differences as weighing against the combination suggested by the Examiner.

The Wironen reference describes a bone paste that contains thermally crosslinkable gelatin as the carrier for one or more osteogenic components. The gelatin-based composition has

the unique ability to exhibit thermoreversible gelation properties that allow the composition to be a fluid at a temperature above normal body temperature and a solid gel at body temperature (see page 7, line 27- page 8, line 6; page 11, lines 21-26; page 12, lines 9-14). As explained throughout the Wironen reference, the use of a gelatin carrier gives the composition the ability to thermally crosslink over a very small temperature range so that, for example, the composition can be easily extruded from a syringe at temperatures above 40°C, but still form a solid gel at physiologic temperature. The Wironen reference teaches that the gelatin component is used in the form of a solution having a 30-45% (w/w) gelatin concentration and further notes that the final gelatin content of the composition described is about 20-45% (w/w).

The Wironen reference specifically contrasts the teachings therein with a commercialized embodiment of the formulation described in the O'Leary reference. On page 3 of the Wironen reference, a commercially available embodiment of the O'Leary formulation is described as a "non-crosslinkable composition" comprising demineralized bone powder suspended in glycerol, which obviously would not exhibit the thermoreversible gelation property described in Wironen. Thus, the fundamental properties of the composition in Wironen are markedly different from the properties of the composition described in the O'Leary reference or the Yim reference, and Wironen itself suggests key distinctions between the O'Leary reference and the Wironen formulation. For this reason alone, there would be no motivation to combine the teachings of the Wironen reference with the O'Leary or Yim references.

Further, the specific language in the Wironen reference that discusses cancellous bone makes it clear that the reference only suggests the addition of such a component to the gelatin based composition described therein. Specifically, the reference suggests that "[t]he composition according to this invention...may act as a carrier for cortical, cancellous, or cortical and cancellous bone chips." (page 13, lines 11-14)(emphasis added). The reference goes further to suggest that "such compositions are useful for fulfilling larger bone voids." (page 13, line 14)(emphasis added). Thus, it is clear that the Wironen reference only suggests the addition of cancellous bone to a gelatin based composition of the type described therein, meaning the composition exhibits thermoreversible gelation properties that are crucial to the invention described in Wironen.

Neither the O'Leary nor Yim references are directed to gelatin-based compositions exhibiting thermoreversible gelation characteristics. The Examiner's reliance on the teaching in O'Leary that gelatin can be added as a thickener in certain embodiments is irrelevant because it does not change the basic and stark distinctions between the characteristics of the O'Leary composition and the Wironen composition. There is nothing in O'Leary to suggest adding the amount of gelatin necessary to create the thermoreversible gelation characteristics described in Wironen. In fact, the O'Leary reference provides absolutely no guidance as to how much gelatin might be added for thickening purposes and it would be completely speculative to suggest that O'Leary could be viewed as teaching the significant amounts of gelatin taught in Wironen. Further, there is certainly nothing in the O'Leary reference to suggest to one of ordinary skill in the art that thermoreversible gelatin based compositions were contemplated. Gelatin was suggested merely in a laundry list of components as a possible thickener to prevent settling of the bone powder from the liquid component of the O'Leary composition. The gelatin reference in O'Leary is completely irrelevant to the teachings of Wironen and irrelevant to the question of whether Wironen is properly combinable with O'Leary in the manner contemplated by the Examiner.

As explained above, Applicants respectfully submit that a fair reading of Wironen would only suggest to one of ordinary skill in the art that cancellous bone chips could be useful as an additive in a gelatin based composition that exhibits thermoreversible gelation properties. For at least the reasons outlined above, Applicants respectfully submit that the three references relied upon by the Examiner in the obviousness rejection are not properly combinable in the manner contemplated in the Office Action. Thus, Applicants respectfully request reconsideration and withdrawal of the rejection and formal notification of the allowability of all claims as now presented.

Applicants submit that even if the three references are properly combinable, which Applicants obviously do not admit, the resulting combination would surely fail to suggest any of the formulations recited in Claims 23-30. Each of said claims recite a specific combination of ingredients including a specific amount of cancellous bone. Even if properly combinable, there is no suggestion in the Wironen/Yim/O'Leary references to form the particular combinations of

ingredients and relative amounts set forth in Claims 23-30. The Wironen reference fails to suggest any concentration level for the optional cancellous bone ingredient. No guidance is provided whatsoever as to the amount of cancellous bone chips, yet the Examiner alleges that each of the combinations recited in Claims 23-30 would be obvious. When dealing with an art that contains absolutely no guidance as to the amount of one claimed ingredient, such an allegation is simply conjecture. Applicants note that the Examiner at least mentions the teachings of the cited art with regard to the amounts of every other claimed ingredient, but fails to explain how one of ordinary skill in the art would arrive at the cancellous bone amounts recited in Claims 23-30. For this additional reason, Applicants respectfully submit that Claims 23-30 are patentable over the cited references.

It is not believed that extensions of time or fees for net addition of claims are required, beyond those that may otherwise be provided for in documents accompanying this paper. However, in the event that additional extensions of time are necessary to allow consideration of this paper, such extensions are hereby petitioned under 37 CFR § 1.136(a), and any fee required therefore (including fees for net addition of claims) is hereby authorized to be charged to Deposit Account No. 16-0605.

Respectfully submitted,



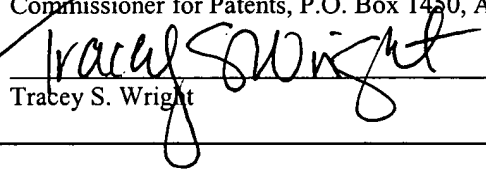
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